Facts on Familial Hypercholesterolemia (FH) and Coronary Heart Disease (CHD)

- FH is a dominantly inherited disease affecting 1 in 500 individuals.
  - Half of all first degree relatives of a patient with FH also suffer from FH.

- FH increases the risk of CHD, especially the risk of premature CHD.
  
  - About 12% of acute myocardial infarction under the age of 60 is due to FH.  
  - About 85% of CHD in severely hypercholesterolemic subjects under the age of 40 is due to FH.
  - 50 fold (in men) to 125 fold (in women) increased risk of fatal myocardial infarction before age 40

- Atherosclerosis associated with FH starts in childhood.

- Timely treatment with statins can delay or prevent CHD.
  
  - Statin therapy in FH patients leads to lowering of cholesterol and regression of atherosclerosis.

- Two-year studies indicate that statin treatment is safe in children

- FH is typically not diagnosed and not treated until middle age

- Family testing for FH can improve diagnosis and treatment levels in children, adolescents, and young adults
  
  - Dutch, Norwegian, and Portuguese programs for screening relatives of FH patients identified on average 2 to 3 affected relatives per index patient and increased treatment levels in recognized patients to 90%.

- The majority of FH is caused by mutations in the genes LDLR or APOB.

- Genetic testing can confirm clinical diagnosis and facilitate family testing
  
  - Genetic testing shows close to 100% sensitivity and specificity in identifying affected relatives of any age. In contrast, sensitivity and specificity of diagnosis based on LDL-cholesterol levels varies with age.

- AHA guidelines consider genetic testing the “criterion standard” for diagnosis of FH in children.
The Impact of FH in the US*

- FH affects an estimated 600,000 Americans.
- With proper diagnosis and treatment, using a combination of targeted genetic testing and lipid-lowering drug therapy:
  - FH related heart attacks could be prevented in 200,000 of these individuals
  - FH-related deaths could be prevented in 50,000 of these individuals.

Using Genetic Testing to Detect Familial Hypercholesterolemia and Increased Risk of Coronary Heart Disease

**Indications:**
- Presence or family history of early-onset coronary heart disease (CHD) (before 45 years in males and before 55 years in females)
- Presence or family history of tendon xanthomas
- Presence or family history of (untreated) total plasma cholesterol levels above 290 mg/dL (7.5 mmol/L) in adults or above 260 mg/dL (6.7 mmol/L) in children under 16 (plasma LDL cholesterol levels above 190 mg/dL (4.9 mmol/L) in adults or above 155 mg/dL (4 mmol/L) in children under 16)

**Benefits:**
- Genetic testing can facilitate
  - diagnosis of Familial Hypercholesterolemia (FH) in relatives of patients.
  - timely treatment to prevent coronary heart disease.

**Background:**
- FH has been linked to atherosclerosis and a dramatically increased risk of early-onset CHD.¹
- FH is associated with autosomal dominant loss-of-function mutations in LDLR or APOB, which occur at a prevalence of 1:500 and 1:1000, respectively.²
- Much of FH-associated CHD can be delayed or prevented through timely treatment.³⁻⁷
- FH is both underdiagnosed and undertreated, especially in the young.⁸⁻⁹
- Family testing can increase diagnosis and treatment levels.¹⁰⁻¹²
- Genetic testing is more sensitive and more specific than biochemical testing for identifying affected relatives of patients.¹⁰,¹³

**References:**

**Ordering Information:** please see other side
Ordering Information for the
LDLR and APOB DNA Sequencing Tests (Early–Onset CHD)

Indications for Testing

- Presence or family history of early-onset coronary heart disease (CHD) (before 45 years in males and before 55 years in females)
- Presence or family history of tendon xanthomas
- Presence or family history of (untreated) total plasma cholesterol levels above 290 mg/dL (7.5 mmol/L) in adults or above 260 mg/dL (6.7 mmol/L) in children under 16 (plasma LDL cholesterol levels above 190 mg/dL (4.9 mmol/L) in adults or above 155 mg/dL (4 mmol/L) in children under 16)

Ordering Information

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>CPT Codes</th>
<th>Test Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>83891(1) 83892(1) 83898(18) 83904(36) 83909(36) 83912(1)</td>
<td>190101</td>
</tr>
<tr>
<td>APOB</td>
<td>83891(1) 83892(1) 83898(1) 83904(2) 83909(2) 83912(1)</td>
<td>190102</td>
</tr>
<tr>
<td>Multi–Gene Panel*</td>
<td>83891(1) 83892(1) 83898(19) 83904(38) 83909(38) 83912(3)</td>
<td>190199</td>
</tr>
</tbody>
</table>

* For the multi-gene panel, a summary report will be issued in addition to an abbreviated report for each individual gene.

Family Testing (single amplicon)

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>CPT Codes</th>
<th>Test Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>83891(1) 83892(1) 83898(1) 83904(2) 83909(2) 83912(1)</td>
<td>190101</td>
</tr>
<tr>
<td>APOB</td>
<td>83891(1) 83892(1) 83898(1) 83904(2) 83909(2) 83912(1)</td>
<td>190102</td>
</tr>
</tbody>
</table>

Test Methodology

- Amplification by polymerase chain reaction (PCR); sequencing of protein-coding region

Sample Requirements

- For blood samples:
  - 2 mL whole blood in EDTA tube (lavender top)
  - Samples can be stored briefly at 4°C, but should be shipped on day of collection.
- For buccal swab samples:
  - Please contact client services at 1-866-647-0735 for instructions.
- All sample types should be shipped overnight at room temperature.
- To request a sample shipping kit, please call 1-866-647-0735.

Turn-around Times

Turn-around times typically range from 7 to 21 days of receipt of sample and all required forms, but may vary depending on test volume and test-specific technical difficulties. Current TATs are posted on our website. Please schedule patient follow-up appointments for discussion of test results conservatively at 6 weeks.

For more information, please contact Correlagen Diagnostics, Inc., at 1–866–647–0735 or visit us on the web at www.correlagen.com.
Familial Hypercholesterolemia and Early-Onset Coronary Heart Disease - an Overview

Introduction

Familial hypercholesterolemia (FH) is a dominantly inherited disease affecting 1 in 500 individuals (see reference 1 for review). FH leads to coronary heart disease (CHD) by age 60 in half of affected men and a third of affected women and causes a 50 fold (in men) to 125 fold (in women) increased risk of myocardial infarction before age 40 (see reference 2 for review). Atherosclerosis due to FH often starts in childhood, but remains asymptomatic until CHD develops (3). While FH is a treatable disease, it is widely under-diagnosed and undertreated, leading to thousands of preventable deaths per year in the US alone (4-7).

Since FH has been linked to autosomal dominant loss-of-function mutations in the genes LDLR or APOB (see reference 1 for review), genetic testing can allow a diagnosis of FH. Genetic “cascade” screening of relatives of FH patients has been shown to be a sensitive, specific, and cost effective method for increasing diagnosis and treatment levels for FH (8-11).

Molecular Pathophysiology

The gene LDLR codes for the low density lipoprotein receptor, which mediates clearance of low-density lipoprotein (LDL), the main plasma reservoir for cholesterol, from the plasma. Lipoproteins are globular particles composed of a core of triglycerides and cholesterol esters and a surface layer of phospholipids and free cholesterol, into which one or more proteins (apolipoproteins) are inserted. Lipoproteins serve to transport cholesterol and other lipids through the aqueous plasma, allowing exchange of lipids between lipoproteins and cells as well as between different types of lipoproteins. Classification of lipoproteins is based on their specific density, which reflects their protein and lipid composition. Low-density lipoprotein (LDL) is particularly rich in cholesterol and contains one principal apolipoprotein (apolipoprotein B-100 or ApoB). Binding of ApoB, encoded by the gene APOB, to LDLR leads to internalization of the LDLR-LDL complex. While LDLR is subsequently recycled to the membrane, LDL is disassembled into its components. In the liver, cholesterol derived from LDL is excreted in the bile, either as free cholesterol or as bile acid. Cholesterol derived from disassembled LDL also inhibits cholesterol biosynthesis within the cell.

Pathogenic sequence variants in LDLR or APOB decrease the ability of liver cells to clear LDL from the plasma. Excess LDL accumulates in arterial walls, where it is oxidized and taken up in a non-saturable manner by macrophages, leading to development of atherosclerotic lesions and, over time, atherosclerotic plaques.

If only one of the two LDLR genes present in each somatic cell is affected by a mutation (heterozygous FH), the removal rate of LDL from the blood is reduced by half, leading to a doubling in the plasma LDL cholesterol level. If both LDLR genes are mutated (homozygous FH), plasma LDL cholesterol levels are increased fivefold or more. Compound heterozygosity for mutations in one copy of the LDLR gene and one copy of the ApoB gene also lead to more severely elevated plasma LDL cholesterol levels.

Clinical Presentation and Diagnosis

Heterozygous FH often first presents with symptoms of CHD in the fourth or fifth decade of life. Cholesterol levels are elevated from birth, but can overlap with those of the normal population (12). Diagnostic cut-off points are therefore difficult to set, especially in children and adolescents, where cholesterol levels are age-dependent (13). While strict clinical criteria allow high specificity of diagnosis, they
result in low sensitivity. Tendon xanthoma, e.g., are highly diagnostic of FH, but do not affect all patients and often do not develop until later in life (14). Use of relaxed clinical criteria increases the sensitivity of diagnosis, but significantly reduces the specificity (12). Even among family members of FH patients, a diagnosis based on cholesterol measurement alone is missed or wrongly assigned in 10-20% of cases (8,12). In contrast, genetic testing shows close to 100% specificity and sensitivity for identifying carriers among relatives of FH patients, once the familial mutation is known (14). Genetic testing also allows a definitive diagnosis of FH in the proband and is therefore considered the “gold standard” for diagnosis of FH. Cost-effective indications for genetic testing include symptoms of CHD before age 45 in men and before age 55 in women; greatly elevated serum cholesterol levels at any age; and family history of premature CHD or of significant hypercholesterolemia (11). In the proband for a family, sequencing of the entire coding region of \textit{LDLR} is indicated, since hypercholesterolemia-associated mutations are scattered throughout the gene (15). Once a familial \textit{LDLR} mutation has been identified, gene sequencing can be limited to the region where the mutation is located to identify other affected family members among the children, parents, or siblings of the proband. All known hypercholesterolemia-associated mutations in \textit{APOB} are located in a 200-nucleotide region (see reference 1 for review).

Homozygous FH typically presents with planar xanthomata by age six, symptoms of CHD by age 10, and, if untreated, leads to myocardial infarction by age 20.

### References


### Treatment

Treatment options for heterozygous FH include dietary restriction of cholesterol and saturated fat and/or administration of statins (HMG-CoA reductase inhibitors), ezetimibe (a selective inhibitor of intestinal absorption of dietary and biliary cholesterol), bile acid sequestrants, or niacin. Most of these interventions are aimed at depleting liver cells of cholesterol, which acts as a feedback inhibitor of \textit{LDLR} expression. Lower levels of cholesterol in the liver cells lead to an increase in the number of \textit{LDLR} molecules expressed on the cell surface, improving plasma clearance of LDL. If statins are not tolerated or not effective, ileal bypass surgery to decrease re-absorption of bile acids from the gut or extracorporeal apheresis combined with LDL immunoabsorption may be considered. Homozygous FH is treated with extracorporeal apheresis or liver transplantation.

Diet and lifestyle changes are generally recommended as the first-line treatment for hypercholesterolemia, especially in children. However, in individuals with FH, diet and lifestyle changes alone are rarely effective, and pharmacological intervention may have to start in childhood (see reference 16 for discussion). Statin therapy has been shown to lead to significant regression of existing carotid atherosclerosis in both children and adults with pathogenic mutations in \textit{LDLR} or \textit{APOB}, and no adverse effects on growth, sexual maturation, hormone levels, or liver or muscle tissue were observed during up to two years of statin treatment in children (17-21).


Requisition Form

Please send sample and completed forms to:
(Ship sample overnight at room temperature.)

Is this a family test for a known familial mutation? □ yes □ no

Gene (eg, MYH7) □ Variant (eg, c.746G>A) □ Exon (eg, x9)

Was the index patient* tested at Correlagen? □ yes □ no
("Family member in whom familial mutation was identified.
If yes: Please complete Index Patient Section on right.

Familial mutation

Information on Index Patient
(if other than current patient)

Name: □ First Name □ MI □ Last Name
Date of Birth: / / month day year
Accession #

Ordering* Check List:
□ Requisition Form (required)
□ Survey (requested)
□ Test Selection Form (required)
□ Payment Form (required)
□ Letter of Medical Necessity (requested for patients with commercial insurance)
□ Clinical Information Form (recommended)
□ Informed Consent (required)

● Catalogue Page and FAQ Flier (for your information only)

For more information, please call: 1-866-647-0735

Cancellation Policy:
Cancellation requests must be submitted in writing by the ordering physician. Cancellation requests will only be accepted if received before specimen testing begins.

* For testing in the fields of endocrinology and metabolism, please order from Athena Diagnostics, Inc.
Dear client,

Please take a moment to fill out this survey. Your responses will help us to serve you even better in the future.

Thank you from your Correlagen team.

How did you hear about us?

- Through a colleague
- Through a patient
- Through a patient advocacy group
- Through the news media
- Through the internet
  - Search engine (such as Google, Yahoo, etc)
  - Google Ad
  - Other:
- Through an e-mail from us
- Through a phone call from us
- Other:

Have you ordered from us before?

- Yes
  - How would you rank our services? Please circle one number (1=unsatisfactory; 5=excellent)
    - Client services 1 2 3 4 5
    - Billing 1 2 3 4 5
    - Turn-around times 1 2 3 4 5
    - Result reports 1 2 3 4 5
    - Informational material 1 2 3 4 5
- No

Which other genetic tests would you like us to offer?


Other comments:


Would you like someone to call you to discuss your responses?

- Yes
- No
### Cardiology

**Atrial Septal Defect with Atrioventricular Block**
- # 190501 TNN2, MYBPC3, MYH7, TPM1, ACTC
- # 190502 TNNT2
- # 190503 TNNT2
- # 190504 MYBPC3
- # 190505 MYH7
- # 190506 ACTC

**Dilated Cardiomyopathy**
- # 190599 TNNT2, MYBPC3, MYH7, TPM1, ACTC
- # 190601 TNNT2
- # 190602 TNNT2
- # 190603 TNNT2
- # 190604 MYBPC3
- # 190605 MYH7
- # 190606 ACTC

**Early-Onset Coronary Heart Disease**
- # 190199 LDLR, APOB
- # 190198 LDLR
- # 190197 APOB

**Hypertrophic Cardiomyopathy**
- # 190938 TNNT2, MYBPC3, MYH7
- # 190938 TPM1, TNNT2, MYB2, MYL3, ACTC
- # 190938 TNNT2, MYBPC3, MYH7, TPM1, TNNT2, MYL2, ACTC
- # 190938 TNNT2, MYBPC3, MYH7, TPM1, TNNT2, MYL2, ACTC
- # 190938 PRKAG2, LAMP2
- # 190350 Reflexive-testing option: TNNT2, MYBPC3, MYH7

**Marfan Syndrome**
- # 190601 FBN1

**Pulmonic Stenosis**
- # 190201 PTPN11

### Nephrology

**Renal Cell Carcinoma**
- # 170101 VHL

**Renal Cysts and Diabetes (RCAD)**
- # 170201 TCF2

### Ophthalmology

**Retinal Degeneration**
- # 180199 BBS1, BBS2
- # 180101 BBS1
- # 180102 BBS2

**Retinal Hemangioblastoma**
- # 180201 VHL

### Immunology

**Hyper IgM Syndrome (HIGM)**
- # 100197 AICDA, UNG, CD40, CD40LG
- # 100199 AICDA, UNG
  - # 100101 AICDA
  - # 100102 UNG
  - # 100103 CD40
  - # 100104 CD40LG

**Severe Combined Immunodeficiency (SCID, SCID/OS)**
- # 100499 IL2RG, JAK3
  - # 100498 IL2RG, ADA, IL7R
  - # 100497 IL2RG, JAK3
  - # 100496 IL2RG, JAK3

**Wiskott Aldrich Syndrome**
- # 100501 WAS

**Hypohydrotic Ectodermal Dysplasia (HED-D)**
- # 100601 IKBG (NEMO)

**Common Variable Immunodeficiency (CVID)**
- # 100701 TNFRSF13B (TACI)

**Chronic Granulomatous Disease, X-linked (XCGD)**
- # 100801 CYBB

**Interferon-γ Receptor Deficiency (IFNGRD)**
- # 100999 IFNγR1, IFNγR2
  - # 100901 IFNγR1
  - # 100902 IFNγR2

**X-Linked Lymphoproliferative Disease (XLP)**
- # 101001 SH2D1A

**Autoimmune Disease or CMC**
- # 110101 AIRE

---

- For testing in the fields of endocrinology and metabolism, please order from Athena Diagnostics, Inc.
- All tests are DNA sequencing tests.
- For multi-gene panels, a summary report will be issued in addition to an abbreviated report for each individual gene.
- The same test code applies to proband and single- or dual-amplicon family testing.
Payment Form

Patient Name
First  Mi  Last

Institutional Billing
Institution Name
Billing Contact
Billing Address
Number  Street  Bldg/Ste
City  State  Zip

Client Authorization #
Phone (   )
Fax (   )
E-mail

Commercial Insurance Billing
Correlagen has established the Capped Patient-Payment Plan (CPPP) to assist patients covered by most commercial insurance. The CPPP limits the financial responsibility of the patient to 15% of the total cost plus any portion of the test cost that is applied by the insurance company to the patient's annual deductible. To participate in the CPPP, patients must be pre-qualified prior to testing (contact a Client Services Representative to get pre-qualified). Once pre-qualified, patients need to complete the information below and provide the 15% payment before testing is initiated. Patients choosing not to participate in the CPPP will be responsible for all charges not covered by their insurance carrier within 60 days of claim submission.

Note: a higher CPPP rate applies for family testing. See http://www.correlagen.com/resources/billing.jsp for CPPP details and exceptions.
1Commercial insurance does not include programs such as Medicare, Medicare HMOs, Medicaid, or Tricare/Champus.

Subscriber Name
First  Last

Insurance Carrier

Membership ID #

Group/ Policy #

Claims Mailing Address
Number  Street  Bldg/Ste
City  State  Zip

UPIN #

**Please include a copy of both sides of the insurance card (required).**

Authorization to Release Information and Pay Benefits: I authorize Correlagen Diagnostics, Inc., to release all information necessary for reimbursement to my designated insurance carrier. I authorize that benefits under this claim be paid directly to Correlagen Diagnostics and will remit any insurance payments that I receive to Correlagen. I acknowledge responsibility for 100% of the service price if I fraudulently represent insurance. In the event of underpayment or denial by my insurance carrier, I authorize Correlagen or its designee to appeal on my behalf to overturn the denial or receive reimbursement for the underpaid claim.

2Correlagen and/or its designee may perform this appeal on my behalf, but is not obligated to do so.

Payment by Check/Credit Card

Check or money order enclosed  $ 

Credit Card

Master Card  Visa  Card Number  Expiration Date  Month  Year
Name as it appears on card

Billing Address
Number  Street  City  State  Zip

Please bill my credit card for the amount of  $

Signature (required)  Date

Copyright © 2006, 2007, 2008 Correlagen Diagnostics, Inc. All rights reserved
Payment Form 04/08
To
Name of Insurance Company:_______________________________________________________

Request for coverage of diagnostic DNA-sequence analysis of the genes

☐ LDLR  ☐ APOB
for the purpose of
☐ confirming a diagnosis of Familial Hypercholesterolemia
☐ evaluating presence or absence of a familial mutation known or believed to be associated with Familial Hypercholesterolemia.

Indicated by
☐ presence or history of clinical symptoms of Familial Hypercholesterolemia:
__________________________________________________________________________

☐ family history (indicative) of Familial Hypercholesterolemia

Regarding my patient
Name of patient: ______________________________________________________________
Insurance number of patient: ______________________________________________________
Name of primary insurance holder: ______________________________________________
Group Policy Number: __________________________________________________________

Familial Hypercholesterolemia (FH), which occurs at a prevalence of 1 in 500, is associated with coronary heart disease (CHD) in half of all affected individuals and a 50-fold (in men) to 125-fold (in women) increased risk of a fatal myocardial infarction before age 40. Atherosclerosis due to FH often starts in childhood, but remains asymptomatic until CHD develops. Risk of CHD can be reduced by timely pharmacological intervention, which has been shown to lead to significant regression of existing carotid atherosclerosis in both children and adults with FH. In contrast to other forms of hypercholesterolemia, FH rarely responds to diet and lifestyle changes, generally recommended as first-line treatment for hypercholesterolemia, and may require more aggressive dosing of medication. Since FH has been associated with mutations in the genes LDLR or APOB, genetic testing can confirm a clinical diagnosis of FH. Genetic testing also facilitates family testing for this dominantly inherited disease. Once the familial mutation has been identified in the index patient for a family, genetic testing can identify family members affected with or predisposed to FH (mutation carriers) and family members who are not at increased risk for FH (non-mutation carriers). Of note, genetic testing is significantly more sensitive and more specific than biochemical testing for identifying affected family members.

I am choosing Correlagen Diagnostics as the provider of genetic testing services, since this CLIA-certified testing laboratory offers reliable sequencing services, consistent variant analysis, and detailed result reporting with short turn-around times. Since known FH-associated mutations are spread throughout the gene LDLR, Correlagen sequences the entire coding region of LDLR in the index patient. Coding regions are amplified and sequenced in segments (amplicons). If the familial FH-associated mutation is known, only the LDLR amplicon harboring the familial mutation is amplified and sequenced. Since all known hypercholesterolemia-associated mutations in APOB are located in a 200-nucleotide region, only one APOB amplicon is sequenced.

In summary, I believe that genetic testing for FH will allow me to provide better care for my patient and will prove to be a cost-effective measure. Please let me know if you have any further questions.

Sincerely,

_____________________________    _____________________________           _______________       _____
Signature    Name (printed)    Tel. No. Date

Letter of Medical Necessity - FH 12/06
Clinical Information Form (Early-Onset Coronary Heart Disease)

Patient:

<table>
<thead>
<tr>
<th>First Name</th>
<th>MI</th>
<th>Last Name</th>
</tr>
</thead>
</table>

Medical History:

- Cardiovascular disease
  - Myocardial infarction
  - Stroke
  - Claudication
  - Xanthomas / xanthelasmas
  - Obesity
  - Type 2 diabetes
  - Metabolic syndrome
  - Cigarette smoking
  - Other (please specify)

<table>
<thead>
<tr>
<th>Medical History</th>
<th>yes</th>
<th>no</th>
<th>Age at onset</th>
<th>Comments</th>
</tr>
</thead>
</table>

Physical Examination Data:

- Height
- Weight
- Blood pressure

<table>
<thead>
<tr>
<th>Physical Examination Data</th>
<th>Date</th>
<th>Value</th>
<th>Comments</th>
</tr>
</thead>
</table>

Laboratory Test Results:

- Total serum cholesterol
- Serum LDL
- Serum HDL
- Serum triglycerides
- Lp(a)
- Other (please specify)

<table>
<thead>
<tr>
<th>Laboratory Test Results</th>
<th>Date</th>
<th>Value</th>
<th>Comments</th>
</tr>
</thead>
</table>

Current Therapy:

- Statin
- Other (please specify)
- Other (please specify)

<table>
<thead>
<tr>
<th>Current Therapy</th>
<th>Start Date</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
</table>

Family History:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Cardiovascular Disease</th>
<th>Age at onset</th>
<th>Hypercholesterolemia</th>
<th>Age at onset</th>
</tr>
</thead>
</table>

Comments:
Informed Consent for Genetic Testing

I hereby request genetic testing by DNA sequencing for the following condition:

________________________________________________________________________________

I understand that the purpose of the DNA test is to look for the presence of abnormalities (often called “variants” or “mutations”) in one or more genes that may be associated with the condition specified above.

I understand that a sample of blood will be obtained from me and/or members of my family by removing blood from a vein, a procedure that carries very little risk. I give permission to collect blood samples from my minor children, named below, to be used for DNA testing for the condition specified above:

<table>
<thead>
<tr>
<th>Child’s Name</th>
<th>Date of Birth</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I understand and agree that:

1. By signing this consent, I authorize my doctor to forward my blood, DNA, or tissue sample as well as relevant clinical information about me and about members of my family to Correlagen Diagnostics, Inc. I understand that the testing laboratory needs this clinical information to provide the most accurate interpretation of my test results.

2. While genetic testing is a valuable tool, it does not always give a definite answer. In some cases, the DNA test may not detect an abnormality, although an abnormality may still be present. This event may be due to an inability of the current technology to identify certain types of abnormalities in the gene(s). In other cases, the significance of an abnormality detected by the DNA test for the condition specified above may be uncertain. Thus, the DNA test is not 100% accurate, and the significance of the results will be reported as a probability of association with the condition specified above. Consulting a doctor or genetic counselor is recommended to learn the full meaning of the results.

3. DNA testing performed on a child and a child’s parents might discover non-paternity (a situation where the acknowledged father is not the biological father) or some other previously unknown information about family relationships, such as adoption.

4. The results of this test will be released only to the physician ordering the test or to persons designated by me, in writing, unless otherwise required by law.
5a. Correlagen Diagnostics, Inc. may contact me if it subsequently learns new information that affects the interpretation of previously reported test results. Correlagen Diagnostics, Inc. will make reasonable efforts to contact me through the physician that ordered the test, unless I designate in writing another person authorized to be contacted.

5b. I indicate my desire to opt out of being contacted if Correlagen Diagnostics, Inc. subsequently learns new information that affects the interpretation of previously reported test results by checking this box: ☐

6a. After DNA testing is completed, all identifiers may be removed from a portion of my sample and from my clinical information and both may be used anonymously for research purposes. I understand that the use of my anonymized sample and clinical information for research purposes may contribute to the identification of new genes, the creation of new diagnostic tests or new medicines, or other events that may be commercially valuable and that I will not receive any financial benefits from such developments.

6b. I indicate my desire to opt out of having my anonymized sample and clinical information used for research purposes by checking this box: ☐. Refusal to permit use of my anonymized sample and clinical information for research purposes will not affect this test procedure.

7. Participation in DNA testing is completely voluntary, and the decision to consent to or to refuse the above testing is entirely mine.

8. My signature below indicates that I have read, or had read to me, the above information and that I understand it. I have had the opportunity to discuss the information, including the purposes and possible risks of genetic testing, with my doctor or someone my doctor has designated. I know that I may obtain professional genetic counseling before signing this consent if I wish. I have all the information I want, and all of my questions have been answered.

______________________________  ____________________________
Signature                                       Date

______________________________
Printed Name

Physician/Counselor Statement: I have explained DNA testing to this individual. I have addressed the limitations outlined above, and I have answered the person’s questions.

______________________________  ____________________________
Signature                                       Date

______________________________
Printed Name

Informed Consent 07/07